IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Kemmerer, Elizabeth
Avi ASHKENAZI, et al.	Art Unit: 1646
Application Serial No. 09/905,056	Confirmation No: 2902
Filed: July 12, 2001	Attorney's Docket No. 39780-1618 P2C44
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On December 23, 2004, the Examiner made a final rejection to pending Claims 39-47 and 49-51. A Notice of Appeal was filed on March 22, 2005, and an Appellants' Appeal Brief was timely filed on October 21, 2005. A Notice of non-compliance was mailed on December 23, 2005 and an amended Appeal Brief was filed on January 6, 2006. An Examiner's Answer was mailed on April 4, 2006.

The following constitutes the Appellants' Reply Brief in response to the Examiner's Answer and is timely filed. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

I. *Claim Rejections Under 35 U.S.C §112, First Paragraph*

Concerning the rejection of Claims 39-43 under 35 U.S.C. §112 as allegedly lacking enablement, the Examiner cites the following arguments in the Examiner's Answer:

(1) The Examiner acknowledges that the instant specification is enabling for an isolated polypeptide having at least 80% amino acid sequence identity to: (a) the amino acid sequence of the polypeptide of SEQ ID NO: 292; or (b) the amino acid sequence of the polypeptide of SEQ ID NO: 292, lacking its associated signal peptide; (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 292; or (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209439, which isolated polypeptide has the activity of inhibiting VEGF stimulated proliferation of endothelial cells, or inducing apoptosis in endothelial cells (see page 3, lines 15-21 of Examiner's Answer).

But the Examiner alleges that the specification "does not reasonably provide enablement for other variants of SEQ ID NO: 292" (page 3, lines 21-22 of Examiner's Answer). The Examiner maintains, and Appellants respectfully disagree for the reasons set forth below, that "toxins or irritants, such as lye or poison ivy extract, would also test positive in this (SVP- skin vascular permeability) assay. Lye and poison ivy extract are not considered to be therapeutically useful" ((page 6, lines 3-5 of the Examiner's Answer). The Examiner further asserts that "just because a substance tests positive like an irritant or toxin in the assay does not mean that the substance plays a role in inflammatory disease. There is no evidence of record linking a change in amount or form of PRO331 with any specific inflammatory response in the body" (page 13, lines 8-12 of the Examiner's Answer). The Examiner maintains the position that finding a positive testing of PRO331 polypeptides in SVP assay is, at the most, a motivating invitation for further research, experimentation and confirmation as to whether PRO331 is useful as a novel proinflammatory cytokine for the treatment of a pathological condition. The Examiner then concludes that "the issue is whether or not undue experimentation would have been required to the skilled artisan to make and use the claimed invention" (page 12, lines 2 and 3 of the Examiner's Answer).

(2) In addition, the Examiner does not find the Declaration by Dr. Sherman Fong, submitted by the Appellants, persuasive allegedly because "it is believed that the opposing

evidence and scientific reasoning counterbalance the evidence contained in the declaration" (page 27, lines 15-19 of the Examiner's Answer).

Initially, Appellants submit that since the 'how to use' prong of the enablement requirement under 35 U.S.C. §112, first paragraph incorporates as a matter of law, a requirement that the specification disclose a practical utility, the utility requirements under 35 U.S.C. §101 are also discussed in the arguments below.

Appellants respectfully submit that an Applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in threat to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. 288, 297 (C.C.P.A. 1974). *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977). Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The Examiner has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Appellant to provide rebuttal evidence. *Id.*

Arguments

(1) Appellants maintain that there is no logical basis for the Examiner's conclusion that PRO331 is an "irritant" because, by definition, irritants need prior exposure in order to elicit an immune response. In this instance, the animal (guinea pig) used in the SVP assay was not pre-

exposed or sensitized to PRO331 and yet, it elicited an inflammatory response in the SVP assay, in response to PRO331. Therefore, such a showing is evidence that PRO331 is not an irritant, but rather an inflammatory molecule. Appellants have discussed this point throughout prosecution and in the Appeal brief filed January 6, 2006. The SVP assay is well-known in the art for identifying inflammatory molecules. Appellants provided a Declaration by Dr. Sherman Fong to discuss the SVP assay, the state of the art in the field of inflammation and provided several examples of use of the SVP assay by other investigators in the art for identifying potential inflammatory molecules. Yet, the Examiner continues to allege and maintain that PRO331 is an "irritant" and proceeds to erroneously conclude that "irritant molecules" are "not considered to be therapeutically useful."

The Examiner's misconceptions regarding the field of inflammation as a whole is further apparent in the cited references against the Appellant, namely, Barsoun *et al.* (*J. Antimicrobial Chemotherapy* 40: 721-724 (1997)), which describes a hypersensitive response in a mouse, and Szalai *et al.* (*J. Immunology* 164: 463-468 (2000)), which describes the Arthus reaction in guinea pigs, and alleges that these assays are similar to the instantly described SVP (assay #64). Appellants strongly disagree with the Examiner's conclusions in this rejection because, again, hypersensitive reactions, by definition, need prior exposure in order to elicit an immune response. As discussed above, the animals in the SVP assay were <u>not</u> presensitized to PRO331 in the SVP assay. Therefore, the teachings of Barsoun *et al.* and Szalai *et al.* do <u>not</u> apply in this instance, and these are <u>improper references for basing this rejection</u>. The Examiner hence has failed to meet the initial burden of offering evidence. Instead. Appellants add that, based on the teachings in the art and the disclosure within Example 77 in the instant specification (that provides meaningful results and guidance that the PRO331 polypeptides tested positive in the SVP assay and is therefore useful as a proinflammatory molecule), the assertion that PRO331 "enhances or induces an immune response" would also be considered credible by a person of ordinary skill in the art.

Even assuming that the Examiner has met the initial burden to offer evidence, which Appellants do not concede with, that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence, *i.e.*, the Rampart *et al.* (*Am J Pathol* **135(1)**:21-25 (1989)) that identified IL-8 using a rabbit skin neutrophil accumulation assay similar to the present SVP assay. Rampart *et al.* suggested the involvement of endogenous IL-8 in an acute phase inflammatory response of an animal to a microbial stimulus and further disclosed suggestive data supporting its involvement

in psoriasis (see page 24, column 1, last paragraph). Further, the Fong Declaration details the state of the art of inflammation and provides art accepted examples of the usefulness for proinflammatory molecules. Therefore, it is more likely than not that those skilled in the art, to a reasonable probability, would believe that the claimed polypeptide is useful because it encodes a proinflammatory molecule, and therefore, are useful for generating antagonistic molecules against PRO331, like antibodies, which are useful to treat diseased conditions involving inflammation.

Yet the Examiner asserts that "the issue is whether or not undue experimentation would have been required to the skilled artisan to make and use the claimed invention."

Appellants respectfully disagree and submit that "(t)he mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility." M.P.E.P. §2107.01 III cites *In re* Brana, 51 F.3d 1560, 34 U.S.P.Q. 2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law....necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is readily to be administered to humans." Further, "to violate §101, the claimed device must be totally incapable of achieving a useful result." *Juicy whip Inc. v. Orange Bang Inc., 51* U.S.P.Q. 2d 1700 (Fed. Cir. 1999), *citing Brooktree corp. v. Advanced Micro devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992). Therefore, the Examiner's interpretation that, patentability precludes any further experimentation is incorrect.

Moreover, the SVP assay is an *in vitro* assay for identifying potential inflammatory molecules. In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a Examiner decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

The *Fujikawa* case was in the context of utility for pharmaceutical compounds and the principals stated by the Court are applicable in the instant case. Utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility. In this instance, there is "sufficient correlation" between a positive result in the SVP assay (*i.e.,* a proinflammatory molecule) and utility in disease conditions like cancer and autoimmune disease.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, *i.e.,* there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Appellant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Accordingly, in view of the disclosure of the present application, one of ordinary skill in the art would understand how to make and use the claimed nucleic acids without undue experimentation.

(2) The Examiner asserts regarding the Fong Declaration that "it is believed that the opposing evidence and scientific reasoning counterbalance the evidence contained in the declaration." For the reasons set forth above under Item (1), the Examiner's reasoning is flawed and the supposedly "opposing evidence" do not apply. Further, as stated in the M.P.E.P., Appellants' rebuttal evidence (the Fong Declaration) does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Therefore, Appellants submit that the present application discloses the utility of the subject matter of the instant claims and that one of skill in the art would know exactly how to use the claimed nucleic acids, for instance, in expressing polypeptides effective for inducing inflammation and for preparing antibodies to reduce inflammation, without any undue experimentation. The specification provides detailed guidance as to how to identify and make nucleic acids encoding polypeptides having complete amino acid sequence identity to PRO331 polypeptides. The specification also provides ample guidance to allow the skilled artisan to identify those polypeptides which meet the limitations of the claims, found in Example 77 (page 210, lines 22) which describes a dye-based proinflammatory cell infiltration assay in which PRO331 polypeptides induce inflammation, or as "inducing mononuclear cell, eosinophil and PMN infiltration at the site of injection of the animal" (page 210, lines 23-24 of the specification). Accordingly, in view of the disclosure of the present application, one of ordinary skill in the art would understand how to make and use the claimed nucleic acids without undue experimentation.

Accordingly, this rejection of Claims 39-43 should be withdrawn.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of claims 39-43.

Respectfully submitted,

Date: June 5, 2006

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